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A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

Statistical Analysis Plan

Version: 2.0

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	09OCT2020	New document
1.1	23JUN2021	1. In Section 4.2, added more details in pretreatment Hb derivation. 2. In Section 4.9, clarified the best 8-week (16-week) interval definition. 3. Added End of Treatment visit in starting date of TI and transfusion reduction interval calculations. 4. In Section 4.7, added 30 days to the last dose date in the definition of concomitant medication. 5. In Section 4.2.3, added a scenario in the imputation rule when the onset of an AE is missing both day and month.
1.2	13APR2021	1. Modified the Ventricular Repolarization (QTc) substudy in Part 2 to separate it from the main study per Protocol Amendment 7.
1.3	24JUN2022	1. Clarified biomarker analysis sets definition. 2. Separate PRO analysis from main study SAP to PRO SAP. 3. Clarified a few subgroup factors and cutoff values in 4.9.1.4 Examination of Subgroups and added baseline platelet and neutrophils. 4. Clarified section 4.9.1.4 to all subgroup factors will be based on values recorded on the eCRF. 5. Clarified 4.9.3.1 Variables Definition for Progression Free Survival (PFS) and Time to progression to AML. 6. Removed "*manual absolute peripheral blast count*" from section 4.10.3.
2.0	15SEP2022	1. Removed PRO measures from secondary endpoints and sequential hypothesis testing per discussion with FDA. Consider PROs as exploratory endpoints that will be descriptively summarized. 2. Clarified the timing of unblinding in Section 3.1. 3. Add Added ALT or AST >3.0 x ULN WITH Bilirubin >2.0 x ULN as adverse event of interest in Section 4.10.2 per Protocol Amendment 6. 4. Clarified Part 1 refers to Phase 2 part and Part 3 refers to Phase 3 part of the study throughout the document.

		5. Clarified that the primary efficacy analysis is planned 12 months (and no longer 15 months) after the last subject is randomized in the main study of Part 2 per Protocol Amendment 7. 6. Clarified the IRC responsibilities per IRC charter v2.0.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
AnS	anemia subscale
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BM	bone marrow
C1D1	Cycle 1 Day 1
CI	confidence interval
Cmax	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EPO	erythropoietin
EQ-5D-5L	EuroQol-EQ-5D-5L
ER	exposure response
ESA	erythropoiesis-stimulating agent

Abbreviation / Acronym	Definition / Expansion
EWB	emotional well-being
FAB	French-American-British
FACT-An	Functional Assessment of Cancer Therapy - Anemia-Related Effects
FACT-An TOI	FACT-An Trial Outcome Index
FWB	functional well-being
Hb	hemoglobin
HEC	Hepatic Expert Committee
HI-E	hematologic improvement-erythroid
HI-N	hematologic improvement-neutrophil
HI-P	hematologic improvement-platelet
HMA	hypomethylating agent
hTERT	human telomerase reverse transcriptase
INR	international normalized ratio
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRC	Independent Review Committee
ITT	intent to treat
IWG	International Working Group
IWRS	Interactive web response system
LFT	liver function test
MAR	missing at random
mCR	Marrow complete remission
MDS	myelodysplastic syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal important difference
MITT	Modified ITT
MMRM	mixed-effects model with repeated measures
Modified IWG 2006	Proposed modification of IWG 2006 response criteria in myelodysplasia

Abbreviation / Acronym	Definition / Expansion
NCI	National Cancer Institute
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression free survival
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PP	Per Protocol
PR	partial remission
PRO	patient-reported outcome(s)
PT	preferred term
PWB	physical well-being
QTc	corrected QT interval
QUALMS	Quality of Life in Myelodysplasia Scale
QUALMS-BF	QUALMS Benefit Finding
QUALMS-E	QUALMS Emotional Burden
QUALMS-P	QUALMS Physical Burden
RBC	red blood cell
SAP	Statistical Analysis Plan
SAE	serious adverse event
SD	standard deviation
SI	System International
SOC	system organ class
SWB	social/family well-being
TA	telomerase activity
TEAE	Treatment-emergent AEs
TI	transfusion independence
TL	telomere length
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This study is designed to evaluate the efficacy and safety of imetelstat in transfusion-dependent subjects with low or intermediate-1 risk myelodysplastic syndrome (MDS) that is relapsed / refractory to erythropoiesis-stimulating agent (ESA) Treatment.

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses for the primary, secondary and exploratory endpoints. It describes the final reporting for study MDS3001 as per protocol amendment #7 dated as September 2, 2021. Safety data to be reviewed by the Data Monitoring Committee (DMC) periodically are specified in the DMC SAP, which is specifically prepared for DMC reviews.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

Part 1 (Phase 2): To evaluate the efficacy and safety of imetelstat in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

Part 2 (Phase 3): To compare the efficacy, in terms of red blood cell (RBC) transfusion independence (TI), of imetelstat to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

2.2 Secondary Objective(s)

- To assess the safety of imetelstat in subjects with MDS
- To assess the time to RBC TI and duration of RBC TI
- To assess the rate of hematologic improvement
- To assess the rates of complete remission (CR), partial remission (PR), or marrow complete remission (mCR)
- To assess overall survival (OS)
- To assess progression free survival (PFS)
- To assess time to progression to acute myeloid leukemia (AML)
- To assess the rate and amount of supportive care, including transfusions and myeloid growth factors (Part 2 only)
- To evaluate the pharmacokinetics and immunogenicity of imetelstat in subjects with MDS
- To assess the effect of treatment on medical resource utilization (Part 2 only)
- To assess the effect of imetelstat on corrected QT (QTc) interval in subjects in the Ventricular Repolarization substudy (to be reported separately from Part 2)

2.3 Exploratory Objective(s)

- To assess the effect of imetelstat treatment on patient-reported outcomes (PROs)
- To evaluate pharmacodynamic biomarkers such as telomerase activity (TA), telomere length (TL) and human telomerase reverse transcriptase (hTERT) and to explore the association between baseline results and clinical response
- To evaluate change of cytogenetic abnormalities and explore the association between baseline cytogenetic status and clinical response
- To evaluate baseline mutational status and mutation changes during treatment for exploring the association with clinical response
- To explore the effects of imetelstat on immune profiles through immunophenotyping (Part 1 only)
- To evaluate the exposure-response relationship between pharmacokinetics and pharmacodynamic biomarkers, efficacy and safety

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2/3, multicenter study of imetelstat in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment. The study will consist of 2 parts, and approximately 270 subjects will be enrolled (57 subjects were enrolled in Part 1(Phase 2), approximately 170 subjects will be enrolled in the main study in Part 2 (Phase 3), and approximately 45 subjects will also be enrolled in a separate Ventricular Repolarization substudy).

Part 1 was an open-label, single-arm Phase 2 design to assess the efficacy and safety of imetelstat. 57 subjects including the expansion cohort were enrolled and followed up for safety, hematologic improvement and reduction in transfusion requirement. The sponsor has reviewed and assessed all available data in Part 1, including blood counts, transfusion requirement, tolerability, pharmacokinetics, and pharmacodynamic biomarker data prior to initiating Part 2.

The futility criteria before Protocol Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (e.g. transfusion reduction, erythroid improvement). Upon review of the efficacy and safety data observed with the 7.5 mg/kg dose among 32 subjects in Part 1, a subset of 13 subjects was identified with higher hematologic response rates. These were subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents (HMAs) or lenalidomide. As of Amendment 2, Part 1 was expanded to include only subjects who meet these criteria, with the goal to confirm the safety and efficacy data seen in this subset thus far and to re-confirm the dose. Twenty-five additional subjects with non-del(5q) MDS and without prior exposure to either HMAs or lenalidomide, so called target population, were enrolled for a total of 38 (out of 57 subjects overall enrolled in Part 1).

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat, Part 2 of the study will be initiated in subjects with non-del(5q) MDS and without prior exposure to either HMAs or lenalidomide.

Part 2 is a double blind, randomized Phase 3 design to compare the efficacy of imetelstat with placebo. Approximately 170 subjects will be randomized in a 2:1 ratio to receive either imetelstat or placebo, respectively. Randomization will be stratified by prior RBC transfusion burden (≤ 6 or > 6 units RBC) and by International Prognostic Scoring System (IPSS) risk group (low risk versus intermediate-1 risk). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to Cycle 1 Day 1 (C1D1) for subjects enrolled in Part 1 or the day of randomization for subjects enrolled in Part 2. In addition to the main study of Part 2, a separate Ventricular Repolarization substudy will enroll approximately 45 subjects to be randomized 2:1 to receive either imetelstat or placebo investigating the effects of imetelstat exposure on ventricular repolarization.

The randomization schedule will be prepared by an independent statistician not otherwise involved with this study and will be implemented within an interactive web response system (IWRS). Blinded treatment will be used for Part 2 to minimize the potential influence of treatment assignment knowledge on clinical decision making, and to reduce potential bias during data collection and evaluation of clinical endpoints, thus ensuring the robustness and integrity of the study. It is the intent that all subjects, investigators and study team members, except some required project roles, will remain blinded to treatment group assignment at least until the primary efficacy analysis (12 months after the last subject is randomized in the main study of Part 2) and the database is finalized. Subjects and investigators may be unblinded after primary efficacy analysis depending on the outcome of the primary efficacy analysis, potential DMC recommendations and/or interactions with health authorities. The study data sources with the potential to cause unblinding risks and the required project roles with appropriate restricted access to these data sources, and other measures to prevent the identification of study treatment(s) until all such opportunities for bias have passed, are described in a separate Blinding Maintenance Plan.

The Sponsor will review safety data on an ongoing basis to ensure the safety of the subjects enrolled in the study. All hepatic adverse events (AEs) and liver function test abnormalities will be reviewed at least on a quarterly basis, or more frequently if needed, by an Independent Hepatic Expert Committee throughout the study.

An independent DMC will be established to monitor safety data. The DMC will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. For Part 1 of the study, the DMC performed ad hoc expedited reviews of any ≥Grade 4 hemorrhagic event occurring on the study or any other safety concerns identified by the sponsor. For Part 2 of the study, the DMC will meet periodically and hold ad hoc meetings if required to review unblinded reports for safety as well as efficacy to evaluate risk versus benefit. After each review, the DMC will make recommendations regarding the conduct of the study. The roles, responsibilities and memberships of the DMC and study team are described in a separate DMC Charter.

An independent review committee (IRC) will be established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) and response (CR, PR, mCR, or cytogenetic response) for subjects with >5% baseline bone marrow aspirate blasts based on the central pathology reviewer's assessment. The IRC will assess responses based on the modified IWG Response Criteria 2006 for MDS. The IRC responsibilities, authorities, and procedures will be documented in a charter.

3.2 Endpoints

Additional details and definitions are provided in Section 4.

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the rate of RBC TI lasting at least 8 weeks. The 8-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks (56 days) starting from Study Day 1 until subsequent anti-cancer therapy if any. Study Day 1 is defined as the day of the first dose for subjects enrolled in Part 1 and the day of randomization for subjects enrolled in Part 2. The starting date of 8-week RBC TI duration must be between Study Day 1 and the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurs first, or Study Day 31 if randomized but not treated.

3.2.2 Secondary Endpoints

- Safety of imetelstat in subjects with MDS (eg, incidence, intensity, and type of adverse events, vital signs measurements, clinical laboratory values, ECGs changes, and deaths);
- 24-week RBC TI rate, defined as the proportion of subjects without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1;
- Time to the 8-week (24-week) RBC TI, defined as the interval from Study Day 1 to the first day of the first 8-week (24-week) RBC TI period;
- Duration of RBC TI, defined as the first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period starts;
- Rate of hematologic improvement, including hematologic improvement-erythroid (HI-E), per modified International Working Group (IWG) 2006;
- Rates of CR, PR, or mCR per modified IWG 2006;
- OS, defined as the interval from Study Day 1 to death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up;
- Progression free survival, defined as the time interval from Study Day 1 to the first date of disease progression or death from any cause, whichever occurs first.
- Time to progression to AML, defined as the interval from Study Day 1 to the date of AML diagnosis.
- Amount and relative change in RBC transfusions;

- Rate of myeloid growth factors usage, defined as the proportion of subjects receive any myeloid growth factors starting from Study Day 1; duration of myeloid growth factor administered starting from Study Day 1;
- Pharmacokinetic parameters (eg, C_{max}, AUC_{0-t}), and immunogenicity of imetelstat (eg, antibodies to imetelstat);
- Medical resource utilization data including hospitalization, emergency room visits, and hematology specialist visits (Part 2 only);
- ECG parameters including change in QT interval by Fridericia's correction method (ΔQTcF) in the Ventricular Repolarization substudy (Part 2 only).

3.2.3 Exploratory Endpoints

Exploratory endpoints are not applicable for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7);

- TA and hTERT at baseline and the change from baseline, TL at baseline only;
- Cytogenetic status at baseline and change over time for cytogenetic response;
- Mutation status at baseline and change over time including at the time of suspected response (CR, PR, HI-E [hemoglobin (Hb)]) or pharmacodynamic(s) (PD);
- Immune profiles at baseline and change from baseline (Part 1 only);
- Assessment of Quality of Life in Myelodysplasia Scale (QUALMS), Functional Assessment of Cancer Therapy - Anemia-Related Effects (FACT-An), and EuroQol-EQ-5D-5L (EQ-5D-5L).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Analysis Definitions

4.2.1 Baseline and Phase

Unless specified otherwise, the baseline value is defined as the last non-missing value collected from the local laboratory on or before the first dose of study drug for Part 1 and Part 2. For subjects who have been randomized but not treated with any study drug, the randomization date will be used as the reference date for baseline value calculation. For the purpose of analysis, the term "study drug" refers to imetelstat for Part 1, and imetelstat/placebo for Part 2.

For efficacy analysis that relates with Hb, i.e. HI-E (Hb), pretreatment Hb will be used, which is defined as the average of all the Hb values (from transfusion history, local, and central lab) in the

8 weeks prior to the first dose date, including the value on the first dose date (Part 1 or Part 2) and excluding values that were within 14 days after transfusion (thus considered to be influenced by transfusion) for all treated subjects. If there were no Hb values that met this definition of not being influenced by transfusions, then the baseline value (the last non-missing Hb, or the average if multiple values from the same date, from local or central lab collected on or before the first dose) is used.
For subjects who have been randomized but not treated with any study drug, the last non-missing Hb, or the average if multiple values from the same date, from local or central lab collected on or before the randomization date will be used for pretreatment Hb.

For each part of the study:

Screening Phase: up to 28 days during which subject's eligibility will be reviewed and approved before Study Day 1.

Treatment Phase: extend from Study Day 1 until the date of the last dose. The Treatment Phase will be subdivided by cycles, based on the nominal treatment cycles as recorded on the CRF. Each cycle is planned to be 28 days.

End of Treatment Phase: between date of last dose of study drug +1 day and the End of Treatment Visit, or the earliest of (the last dose date +30 days, death date, or the last contact date if subject lost to follow-up or withdrew consent) when End of Treatment Visit is not performed. The assessments performed during the 'End-of Treatment Visit' will be included in this phase.

Post-treatment Follow-up Phase: Posttreatment Follow-up Phase will continue after the end of treatment phase until death, lost to follow-up, withdrawal of consent, or the End of the Study (whichever occurs first). End of Study is defined as 24 months after Randomization of the last subject in the main study of Part 2 or anytime the sponsor terminates the study, whichever comes first.

Treatment-Emergent Period: In general, the treatment-emergent period is defined as the time from first dose date through 30 days after last dose date, or the day before subsequent antineoplastic therapy, whichever occurs first.

4.2.2 Study Day

Study Day 1 is defined as the day of the first dose for subjects enrolled in Part 1 and the day of randomization for subjects enrolled in Part 2.

Study Day = assessment date – Study Day 1 + 1 for assessments performed **on or after** Study Day 1;
Study Day = assessment date – Study Day 1 for assessments performed **before** Study Day 1;
Cycle Day = assessment date – date of the first dose for the cycle + 1.

All durations are calculated as the stop date minus the start date +1 unless otherwise specified.

4.2.3 Missing or Partial Dates

In general, imputation of partial missing dates will be made for AE onset date, AE resolution date, date of death, start and end dates of concomitant therapy, and date of initial diagnosis.

For AE onset and resolution date, the global standard AE imputation rules listed below will be applied.

- Partial AE onset dates will be imputed as follows:

  - If the onset date of an adverse event is missing day only, it will be set to:
    - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose date;
    - The day of first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different;
    - The day of first dose date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same;

  - If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
    - January 1 of the year of onset, as long as this date is after the first dose date;
    - Month and day of the first dose date, if this date is the same year that the AE occurred;
    - Last day of the year if the year of the AE onset is prior to the year of the first dose date;
    - The AE resolution date;

  - Completely missing onset dates will not be imputed.

- Partial AE resolution dates not marked as ongoing will be imputed as follows:

  - If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month;
  - If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year;
  - Completely missing resolution dates will not be imputed;

For start and end dates of concomitant therapies, the global standard AE imputation rules listed above will be applied accordingly.

For date of death and date of initial diagnosis, the following rule will be applied.

- If date is completely missing, no imputation will be made;
- If year is missing, no imputation will be made;
- If only year is present, but, month and day are missing, then June 30th will be used;
- If only day is missing but year and month are available, then the 15th of the month will be used;

However, the above imputations will be modified by the following rules:

- If such imputed date for initial diagnosis is on or after study consent date, then consent date - 1 will be used;
- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date + 1 will be used.

4.3 General Presentation Considerations

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place and won't be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from baseline will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "< 0.001". Confidence intervals (CI) will be presented to one more decimal place than the raw data.

In general, the analysis for Part 2 will be conducted by treatment group, for Part 1 by population type. The population type of Part 1 is specified as below:

(1) All subjects: all subjects enrolled in Part 1;

(2) Target population: the subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents (HMAs) or lenalidomide;
(3) Other subjects: all Part 1 subjects excluding the subjects in the target population;

All report outputs will be produced using SAS® version 9.3 or a later version, and other software e.g. R as needed, in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

Disposition information will be summarized for the All Treated analysis set for Part 1 and the ITT analysis set for Part 2 at the end of treatment and at the end of study, respectively. Subject enrollment will be summarized by country and investigator.

Descriptive statistics (mean, SD, median, and range) will be provided for time (in weeks) on study treatment as well as length of follow-up (in months). Time on treatment is defined as the interval between the first dose date and the last dose date or death date (censored) if die before End of Treatment visit. Time on study is defined the same way as OS with reversed censoring, i.e., a subject who died will be censored. Based on this definition, time on study is the same as length of follow up. The Kaplan-Meier method will be used to estimate the median time on treatment and on study.

4.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on subject's right, safety, well-being, and/or the validity of data for analysis. Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Subjects with major protocol deviations will be listed. For Part 1, major protocol deviations will be based on clinical review mainly of the following categories: (1) Entered but did not satisfy eligibility criteria; (2) Developed withdrawal criteria but not withdrawn; (3) Received a disallowed concomitant treatment; (4) Received wrong treatment or incorrect dose; and (5) other. For Part 2, major protocol deviations will be summarized and presented by the classifications in Protocol Deviation Specification.

The number of subjects with major deviations from the protocol will be counted and documented together with their corresponding population type (Part 1) or treatment group (Part 2), and the reason/circumstances leading to the deviation. A summary of the number and percentage of enrolled subjects with a major protocol deviation by population type (Part 1) or randomized

subjects with a major protocol deviation by treatment group (Part 2) and overall, and by type of deviation will be provided.

4.5 Analysis Sets

The analysis sets for Part 1 and Part 2 will be defined separately. And the results for Part 1 and for Part 2 will also be summarized and presented separately. In Part 2, the stratification factors (prior RBC transfusion burden and IPSS risk group) used at the randomization, i.e., values entered into the IWRS, will be used for testing of the primary endpoint and the key secondary endpoints.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to the sponsor for review. An analysis set classification meeting for Part 2 will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding of Part 2 and will be documented and approved by the Sponsor.

A by-subject listing of analysis set details will be provided. This listing should include center, subject identifier, and inclusion/exclusion flag for each set and reason for exclusion from each set. All subjects screened should appear on this listing.

4.5.1 Efficacy Analysis Sets

Part 1 (Phase 2):

All Treated analysis set: includes all subjects who receive at least one dose of study drug. This analysis set will be used for all analyses of efficacy endpoints (except time to the 8 or 24-week RBC TI and duration of RBC TI), analyses of disposition, demographics, and baseline disease characteristics.

All Treated 8-week (24-week) TI responder analysis set: includes all treated subjects who do not have any RBC transfusion during any consecutive 8 (24) weeks starting from Study Day 1 until subsequent anti-cancer therapy if any, with the TI starting date between Study Day 1 and date of last dose of study medication + 30 days or End of Treatment Visit whichever occurs first. This analysis set will be used for analyses for time to RBC TI and duration of RBC TI.

Part 2 (Phase 3):

Intent-to-Treat (ITT) analysis set: includes all subjects randomized into the main study. This analysis set will be used for all analyses of efficacy and patient-reported outcomes (PRO) endpoints (except time to the 8 or 24-week RBC TI and duration of RBC TI), analyses of disposition, demographic, and baseline disease characteristics. Subjects will be classified according to assigned treatment group, regardless of the actual treatment received.

ITT 8-week (24-week) TI responder analysis set: includes all subjects in the ITT analysis set who do not have any RBC transfusion during any consecutive 8 (24) weeks starting from Study Day 1 until subsequent anti-cancer therapy if any, with the TI starting date between Study Day 1 and date of last dose of study medication + 30 days or End of Treatment Visit whichever occurs first. This analysis set will be used for analyses for time to the RBC TI and duration of RBC TI.

Modified ITT (MITT) analysis set: includes all ITT subjects who received at least one dose of study drug according to assigned treatment group. This analysis set will be used for sensitivity analyses for 8-week and 24-week RBC TI in the case there are subjects who were dosed, but didn't receive the assigned treatment.

Per-protocol (PP) analysis set: This analysis set is a subset of the ITT analysis set. Subjects with key protocol deviations will be excluded from the PP analysis set. The categories and terms of the key protocol deviations leading to exclusion are defined in the project-specific Protocol Deviation Specification.

Subjects in this analysis set will be analyzed according to the treatment to which they are randomized. This analysis set will be used for sensitivity analysis for 8-week and 24-week RBC TI.

4.5.2 Safety Analysis Sets

For both Part 1 and 2, the Safety analysis set includes all subjects who receive at least one dose of study drug. This analysis set will be used for all safety analyses and analyses of exposure. All subjects will be analyzed according to the treatment which they actually received.

4.5.3 Biomarker Analysis Sets

For both Part 1 and 2, the Biomarker analysis set includes all subjects who received at least one dose of study drug and had at least one biomarker sample at baseline collected.

4.5.4 Pharmacokinetics (PK)/ Pharmacodynamics (PD) Analysis Sets

For both Part 1 and 2, the PK analysis set includes all subjects who received at least one dose of study drug and had at least one post-dose quantifiable plasma sample. The PD analysis set includes all subjects who had at least one quantifiable post-dose determination on biomarker, efficacy or safety parameters as defined in the related Pharmacodynamics analysis plan.

4.5.5 Ventricular Repolarization Substudy Analysis Sets

The Ventricular Repolarization substudy analysis set includes all subjects who participated in Ventricular Repolarization substudy and received at least one dose of study drug.

4.6 Demographic and Other Baseline Characteristics

All demographic and baseline characteristic variables will be summarized for the All Treated analysis set for Part 1 and the ITT analysis set for Part 2.

The stratification factors used during randomization for Part 2 (prior RBC transfusion burden and IPSS risk group) will be tabulated. And values of prior RBC transfusion burden and IPSS risk group recorded on the electronic case report form (eCRF) will be summarized in transfusion history and disease characteristics as mentioned below. Any discrepancy between two data sources will be summarized as well.

Demographics and baseline characteristic data will be summarized, including sex, age (year), race, Eastern Cooperative Oncology Group (ECOG) performance status, weight (kg), and height (cm).

Hepatitis serology tests at baseline will be summarized by test type and results. Two panels of baseline clinical laboratory tests specified will be summarized: hematology and serum chemistry. Frequencies of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade at baseline will be reported.

Disease characteristics to be summarized will include French-American-British (FAB) classification and World Health Organization (WHO) classification, IPSS risk category (low, intermediate-1), IPSS-R risk category (very low, low, intermediate, high, very high) [3], prior ESA treatment (Yes, No), serum EPO level (≤ 500 mU/mL, > 500 mU/ml), and time since initial diagnosis (month).

Transfusion history summaries will include total RBC transfusion units in the 16 weeks prior to study entry and prior RBC transfusion burden. Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to C1D1 for subjects enrolled in Part 1 or the day of randomization for subjects enrolled in Part 2. Per revised IWG 2018 [4], the low transfusion burden (LTB) subject is who received 3 to 7 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes. The high transfusion burden (HTB) subject is who received ≥8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes.

Medical history will be summarized including abnormality in physical examination. In addition, summaries of bone marrow (BM) findings at baseline will be provided.

4.7 Concomitant Medication

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prestudy, Concomitant, or Subsequent.

Medications that start prior to the date of first dose of study drug will be classified as Prestudy. Medications will be classified as Concomitant if used between the date of first dose of study drug

and the last dose date + 30 days. A medication used after the last dose + 30 days is considered as Subsequent.

Medication will be coded using the latest version Anatomical Therapeutic Chemical (ATC) dictionary. Use of prestudy, concomitant or subsequent medications will be summarized by ATC class and drug generic term. Best response to last line of prior anticancer therapy will also be summarized. By-subject listings of concomitant medication details will be provided.

4.8 Exposure and Treatment Compliance

All exposure summaries are to be presented for the Safety analysis set for Part 1 and Part 2.

Exposure to study drug and reasons for discontinuation will be tabulated. The number of treatment cycles received along with the duration of treatment exposure, dose interval (the days between two consecutive dosing dates), average dose intensity (sum of the dose intensity (mg/kg) received in all cycles divided by the number of cycles), and relative dose intensity (total actual dose / total planned dose) will be summarized.

Summaries will be provided for doses intensity of study drug (mg/kg) and relative dose intensity by cycle.

Descriptive summaries will be provided for dose changes. Reasons for dose changes will be summarized across the study, for each of the following changes: cycle delay (>3 days), dose reduction, and infusion interruption/rate change. Adverse events leading to each type of dose change will be summarized. Summary of time to the first infusion or dose modification (dose reduction, infusion interruption/abortion/rate change, or cycle delay) from the first dose date will also be provided.

A summary table of the duration of the study follow-up will be produced and a by-subject listing of treatment compliance data and a by-subject listing of exposure data will also be provided.

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided nominal significance level of 0.05 and all CIs at a 2-sided level of 95%. The overall type I error rate is 0.05 (two-sided) for the primary and secondary efficacy hypotheses in each part of the study.

Statistical Hypotheses for Trial Objectives

For Part 1 (Phase 2), RBC TI in 5 or more of 30 subjects rejects null rate of 6.5% with a single-arm, one-sided, level 0.05 exact test.

For Part 2 (Phase 3), the primary hypothesis of this study is that the imetelstat will significantly improve the rate of RBC TI as compared to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed or refractory to ESA treatment.

The statistical hypotheses are as follows:

H_0: The RBC TI rate of experimental treatment group and the placebo group are equal.
H_1: The RBC TI rate of experimental treatment group is greater than the placebo group.

The hypothesis will be tested using a stratified Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factors at a two-sided significant level of 0.05.

4.9.1.1 Handling of Missing Data

No imputations for missing data will be made for the primary and secondary efficacy endpoints. The double-blind study design of Part 2 and the symmetric assessment schedule reduce the potential for systematic bias, but the treatment effect may be attenuated by missing transfusion data. In order to be considered transfusion independent, a subject must have completed continuous transfusion assessments throughout the qualifying observation period where his/her transfusion independence is determined. An apparent transfusion free period with one or more missing transfusion assessments will not be considered a qualifying 8-week or 24-week TI period. Subjects with no qualifying observation periods will be considered non-responders.

The number and percentage of subjects with missing data for the primary endpoint will also be summarized by major reason. In addition, a Kaplan-Meier plot of the time to study discontinuation will be provided.

A subject data listing will be provided showing all subjects with missing values for the primary endpoint. For these subjects, the listing will provide the observed data relating to the primary endpoint, important baseline characteristics, the recorded reason(s) for study discontinuation and the timing of study discontinuation.

4.9.1.2 Adjustments for Covariates

For Part 2, the 8-week RBC TI rates will be summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson CIs for the 2 treatment groups. Difference in TI and its 95% CI will be presented using Wilson Score method [1]. The comparison will be based on a stratified CMH test adjusting for the following baseline covariates used for stratified randomization:

1. prior RBC transfusion burden (≤ 6 or > 6 units RBC)
2. IPSS risk group (low risk or intermediate-1 risk)

An 'unadjusted' sensitivity analysis will be performed to assess the robustness of the study results, which is detailed in section 4.9.2.3.

4.9.1.3 Multiple Comparisons/Multiplicity

Testing of Primary Endpoint for Part 2 (Phase 3)

For Part 2, the primary hypothesis is that imetelstat will increase the rate of RBC TI as compared to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment. The primary efficacy hypothesis on 8-week RBC TI will be tested at 0.05 (two-sided) for Part 2.

Testing of Secondary Endpoints for Part 2 (Phase 3)

For Part 2, a sequential gate-keeping procedure and Hochberg procedure will be implemented to ensure that the overall type I error rate for the secondary endpoints is controlled. Let α be the critical type I error rate 0.05 (2-sided). 24-week RBC TI and rate of HI-E per modified IWG 2006 are the most important secondary endpoints, thus will be used as gate keepers and be tested at the α level sequentially. 24-week RBC TI will be the first gate keeper and rate of HI-E per modified IWG 2006 will be the second gate keeper. If the nominal p-value is $< \alpha$ for 24-week TI, then rate of HI-E will be tested next at the α level. If the nominal p-value is $< \alpha$ for rate of HI-E as well, the remaining selected secondary hypotheses (PFS, and OS) will be tested using a Hochberg procedure [2].

In summary, the secondary endpoints as the gate keepers which will be tested sequentially at 0.05 (2-sided) are:

1. 24-week RBC TI
2. Rate of HI-E per modified IWG 2006

If the above two gate keepers are significant, the following endpoints will be tested using a Hochberg procedure:

- PFS
- OS

In general, Hochberg procedure is conducted as the following steps:

1. Suppose we have $H_1, \ldots, H_m$ null hypotheses tested and $P_1, \ldots, P_m$ as their corresponding p-values. We order these p-values in increasing order and denote them by $P_{(1)}, \ldots, P_{(m)}$.
2. For a given significance level α, find the largest k such that $P_{(k)} \leq \alpha /(m+1-k)$.
3. Reject the null hypothesis for all $H_{(i)}$ for i=1, …, k.

Note that Hochberg procedure does not require the order of hypotheses and it controls the overall type I error when conducting multiple comparisons at the given significance level α if the p-values are independent or positively correlated.

4.9.1.4 Examination of Subgroups

Subgroup analyses will be performed to assess the consistency and robustness of the treatment benefit mainly for the rate of RBC TI and the rate of HI-E. Subgroup analysis may be performed for other selected efficacy and safety endpoints. CMH tests between the two treatment groups within each subgroup will be calculated for Part 2.

Note that the following subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

The uniformity of the treatment effect will be examined for, but may not be limited to the following subgroups:

- Sex (male vs. female)
- Age (≤ 65 vs. > 65 years old; ≤ 75 vs. > 75 years old)
- Time since initial diagnosis (< 2 vs. ≥ 2 years)
- WHO Classification (RS+ vs. RS-)
- Prior RBC transfusion burden (≤ 6 vs. > 6 units RBC; <8, 8-12, or >12 units RBC)
- Transfusion burden per IWG 2018 (HTB vs LTB)
- Baseline bone marrow blasts per central lab (≤ 5% vs. > 5%)
- IPSS risk group (low risk vs. intermediate-1 risk)
- Number of cytopenia (0-1 vs. 2-3)
- Prior ESA use (yes vs. no)
- Baseline serum EPO levels (≤ 500 vs. >500 mU/mL)
- ECOG score (0 vs. 1-2)
- IPSS-R Cytogenetic risk groups (very good/good, intermediate, or poor/very poor) [3]
- IPSS-R Prognostic risk groups (very low, low, intermediate, high, or very high) [3]
- Baseline platelets (<150 vs. >=150 x10^9/L)
- Baseline neutrophils (<1.5 vs. >=1.5 x10^9/L)

All factors will be based on values recorded on the eCRF as indicated above.

The corresponding rate and associated 2-sided 95% CIs will be summarized and presented on a forest plot for the 2 treatment groups of Part 2 respectively, along with the results of the overall analysis for Part 2.

4.9.2 Primary Efficacy Variable – 8-week rate of RBC TI

4.9.2.1 Variable Definition

The primary variable for the assessment of efficacy is the rate of RBC TI lasting at least 8 weeks. The 8-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion

during any consecutive 8 weeks (56 days) starting from Study Day 1 until subsequent anti-cancer therapy if any. The starting date of 8-week RBC TI duration must be between Study Day 1 and the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurs first, or Study Day 31 if randomized but not treated.

4.9.2.2 Analysis Methods

The primary efficacy analysis is planned at 12 months after the last subject is randomized in the main study of Part 2, and the final analysis is at the End of the Study defined as 24 months after randomization of the last subject in the main study of Part 2 or anytime the sponsor terminates the study, whichever comes first.

Efficacy data in Part 1 will be descriptively summarized based on the treated population. Efficacy data the main study of in Part 2 will be compared between the imetelstat and placebo groups based on the ITT population. Any available efficacy data from Ventricular Repolarization Substudy will be descriptively summarized in addition to the efficacy data from the main study in Part 2.

Part 1 (Phase 2):
The proportion of subjects with 8-week RBC TI will be summarized with a frequency and percentage along with its 95% 2-sided exact Clopper-Pearson CI. The forest plot of the subgroup (defined in section 4.9.1.4) corresponding rate and associated 2-sided 95% CIs will be presented.

Part 2 (Phase 3):
The 8-week RBC TI rates will be summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson CIs for the 2 treatment groups. Difference in TI and its 95% CI will be presented using Wilson Score method [1]. The comparison will be based on a stratified CMH test adjusting for the stratification factors at a two-sided significance level of 0.05:

1. Prior RBC transfusion burden (≤ 6 or > 6 units RBC)
2. IPSS risk group (low risk or intermediate-1 risk)

4.9.2.3 Sensitivity Analysis

Sensitivity analyses will be performed for Part 2 to evaluate the robustness of the primary analysis and includes:

- CMH test of 8-week based on MITT analysis set in the case there are subjects who were dosed, but did not receive any assigned treatment;
- CMH test of 8-week based on PP analysis set;
- CMH estimate of the odds ratio of 8-week RBC TI with the stratification factors and the associated 95% CI;
- Comparison of 8-week RBC TI based on CMH test adjusted by values of prior RBC transfusion burden and IPSS risk group recorded on the eCRF.

- Comparison of 8-week RBC TI based on CMH test without adjusting for the baseline stratification factors.

4.9.3 Key Secondary Efficacy Variables

4.9.3.1 Variables Definition

24-week RBC TI rate

24-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1 until subsequent anti-cancer therapy if any. The starting date of 24-week RBC TI must be between Study Day 1 and the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurs first, or Study Day 31 if randomized but not treated.

Time to 8-week (24-week) RBC TI

Time to 8-week (24-week) RBC TI is defined as the interval from Study Day 1 to the first day of the first 8-week (24-week) RBC TI period.

Duration of RBC TI

Duration of RBC TI is defined as the first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period starts. Subjects who have not had an RBC transfusion ending the TI period at the time of analysis or who withdraw from the study will be censored at the date of the last transfusion evaluation or the day before the first date of subsequent anticancer therapy if given, whichever occurs first.

Rate of hematologic improvement, including HI-E, per modified IWG 2006

The modified IWG 2006 criteria [5] for HI define specific responses of cytopenia in the three hematopoietic lineages: erythroid (HI-E), platelet (HI-P), and neutrophil (HI-N). Rate of hematologic improvement is defined as the proportion of subjects who achieve HI-E, or HI-P, or HI-N.

HI-E is defined as a hemoglobin (Hb) increase of at least 1.5 g/dL above pretreatment and lasts at least 8 weeks or reduction of at least 4 units of RBC transfusion units/8 weeks compared with the prior RBC transfusion burden. A valid 8-week period must start before the date of last dose of study drug + 30 days or End of Treatment Visit whichever occurs first, or Study Day 31 if randomized but not treated, and ends before the first transfusion in posttreatment follow-up or the first day of subsequent anti-cancer therapy whichever occurs first. Pretreatment Hb level is defined as the average of all the Hb values (from transfusion history, local, and central lab) in the 8 weeks prior to first dose date, including the value on first dose date (Part 1 or Part 2) and excluding values that were within 14 days after transfusion (thus considered to be influenced by transfusion) for all

treated subjects. If there were no Hb values that met this definition of not being influenced by transfusions, then the baseline value (the last non-missing Hb, or the average if multiple values from the same date, from local or central lab collected on or before the first dose) is used. For subjects who have been randomized but not treated with any study drug, the last non-missing Hb, or the average if multiple values from the same date, from local or central lab collected on or before the randomization date will be used for pretreatment Hb.

HI-P is defined as absolute increase in platelet count of ≥ 30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets or increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100% lasts at least 8 weeks.

HI-N is defined as at least 100% increase in neutrophil count and an absolute increase > 0.5 x 10^9/L lasts at least 8 weeks.

Progression or relapse after HI is defined as at least 1 of the following, in the absence of another explanation, per modified IWG 2006: a) at least 50% decrement from maximum response levels in granulocytes or platelets; b) reduction in Hb by ≥ 1.5 g/dL; c) transfusion dependence.

Rate of HI-E per revised IWG 2018

For LTB subjects (who received 3 to 7 RBC units in the 16 weeks prior to study entry):

- Clinically meaningful HI-E response per revised IWG 2018 [4] is defined as 16-week RBC TI, i.e. subjects without any RBC transfusion during any consecutive 16 weeks.

For HTB subjects (who received ≥8 RBC units in the 16 weeks prior to study entry):

- Major HI-E response per revised IWG 2018 is defined as 16-week RBC TI.
- Minor HI-E response per revised IWG 2018 is defined as a reduction by at least 50% of RBC units over a 16-week period compared with the 16 weeks prior to Study Entry.

Rate of Complete remission (CR), Partial remission (PR) or Marrow complete remission (mCR)

It is defined as the proportion of subjects who achieve CR, PR or mCR per modified IWG 2006. The analysis will be performed in the ITT analysis set as well as in subjects with bone marrow blasts > 5% at baseline.

Progression Free Survival (PFS)

Progression free survival, defined as the time interval from Study Day 1 to the first date of disease progression or death from any cause, whichever occurs first. Subjects who received subsequent anti-cancer therapy prior to documented progression will be censored at the date of last evaluable response assessment or disease progression status conducted on or prior to the initiation of subsequent anti-cancer therapy. If subjects do not have any adequate post-baseline assessment and did not die, PFS will be censored at Study Day 1.

PFS will be computed as date of PFS event or censoring – Study Day 1+ 1.

Overall Survival (OS)

OS is defined as the interval from Study Day 1 to death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up.

Time to progression to AML

Time to progression to AML is defined as the interval from Study Day 1 to the date of AML progression. Subjects who received subsequent anti-cancer therapy prior to documented progression will be censored at the date of last evaluable response assessment or disease progression status conducted on or prior to the initiation of subsequent anti-cancer therapy. If subjects do not have any adequate post-baseline assessment, time to progression to AML will be censored at Study Day 1.

Amount and relative change in RBC transfusions

Amount of RBC transfusions per 8-week (16-week) is defined as the total number of RBC transfusion units in a given 8-week (16-week) interval during study.

Relative change in RBC transfusions per 8-week = (amount of RBC transfusions per 8-week – prior RBC transfusion burden) / prior RBC transfusion burden multiply by 100%.

Relative change in RBC transfusions per 16-week = (amount of RBC transfusions per 16-week – total RBC transfusion units in 16 weeks prior to study entry) / total RBC transfusion burden in 16 weeks prior to study entry multiply by 100%.

The starting date of an 8-week (16-week) interval must be between Study Day 1 and date of last dose of study drug + 30 days or End of Treatment Visit whichever occurs first, or Study Day 31 if randomized but not treated, and the ending date must be before the first transfusion in posttreatment follow-up or the first day of subsequent anti-cancer therapy whichever occurs first. Note that prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to Cycle 1 Day 1 (C1D1) for subjects enrolled in Part 1 or the day of randomization for subjects enrolled in Part 2.

Rate of myeloid growth factor usage

Rate of myeloid growth factor usage is defined as the proportion of subjects who received any myeloid growth factors starting from Study Day 1. Duration of myeloid growth factor administered starting from Study Day 1 will also be summarized.

PRO measure of interest

See details in Section 4.11.6.

4.9.3.2 Analysis Methods

Part 1 (Phase 2):

The proportion of subjects with 24-week RBC TI, CR, PR, and hematologic improvement, and other binary endpoints, will be summarized with percentage along with its 95% 2-sided exact Clopper-Pearson CI. The time to 8-week RBC TI and time to 24-week RBC TI will be summarized descriptively based on 8-week and 24-week TI responder analysis set, respectively. The Kaplan-Meier method will be used to estimate the distribution of duration of RBC TI based on 8-week and 24-week TI responder analysis set, respectively. The distribution of OS, PFS, and time to progression to AML will be summarized using similar Kaplan-Meier methods.

Part 2 (Phase 3):

The 24-week RBC TI rates will be summarized with frequencies and percentages along with 2-sided 95% exact Clopper-Pearson CIs for the 2 treatment groups. Difference in TI and its 95% CI will be presented using Wilson Score method [1]. The comparison will be based on a stratified CMH test adjusting for the stratification factors at a two-sided significant level of 0.05.
Sensitivity analyses will be performed for Part 2 to evaluate the robustness of the 24-week RBC TI endpoint and includes:

- CMH test of 24-week RBC TI based on MITT analysis set in the case there are subjects who were dosed, but didn't receive any assigned treatment;
- CMH test of 24-week RBC TI based on per-protocol analysis set;

The time to 8-week and 24-week RBC TI will be summarized descriptively for the 2 treatment groups based on ITT 8-week and 24-week TI responder analysis set, respectively. The Kaplan-Meier method will be used to estimate the distribution of duration of RBC TI based on ITT 8-week and 24-week TI responder analysis set, respectively, and will be compared between two treatment groups using stratified log rank test based on ITT 8-week responder analysis set. The distribution of cumulative duration of RBC TI ≥ 8 weeks (sum of all durations of RBC TI ≥ 8 weeks) will be estimated by Kaplan-Meier based on ITT 8-week responder analysis set as well.

The proportion of subjects with hematologic improvement, CR, PR, or mCR per modified IWG 2006, and other binary endpoints will be evaluated using the same statistical methods as for the endpoint of 24-week RBC TI rates. The 8-week RBC TI rate in the first 24 weeks and 48 weeks (proportion of subjects who had RBC TI ≥ 8 weeks in the first 24/48 weeks) will be evaluated similarly.

The distribution of OS, PFS, and time to progression to AML will be compared using stratified log rank test for ITT analysis set. The Kaplan-Meier method will be used to estimate the

distribution for each treatment. The treatment effect (hazard ratio) and its two-sided 95% CIs are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The reasons for censoring of time to progression to AML will be tabulated.

For both Part 1 and 2, the amount and relative change in RBC transfusions will be summarized descriptively for each treatment group, and the relative and absolute change in transfusion amount in the best 8-week (16-week) interval (defined as an 8-week or 16-week interval where the subject had the fewest RBC transfusions on study) will be illustrated by waterfall plots. The distribution of duration from the start of the first 8-week interval that had ≥ 4 units of RBC transfusion reduction to the End of Treatment visit (or censored at the last dose day if still on treatment) will be estimated by the Kaplan-Meier method based on HI-E responders (transfusion reduction) for each treatment group.

Hemoglobin means, mean changes over time, and Hb rise (defined as the maximum Hb value in the longest transfusion free interval excluding values that were within 14 days after transfusion– the pretreatment Hb level) for subjects who achieved 8-week or 24-week RBC TI will be summarized for each treatment group. The longest transfusion free interval will be also illustrated by waterfall plots and swimmer-lane plots as appropriate.

Summary statistics (N, mean, SD, median, and range) and changes from baseline will be calculated for serum ferritin by scheduled visits for each treatment group. The usage of iron chelation therapy (ICT) will be summarized as well.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Analysis Set as defined in Section 4.5.2. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). Missing safety data will generally not be imputed. As an exception, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

4.10.1 Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest version Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in NCI-CTCAE Version 4.03.

The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, vital signs measurements, clinical laboratory results (hematology and chemistry), and deaths.

Drug-related AEs are those assessed by investigator as being possible, probable or very likely related to study drug.

Treatment-emergent AEs (TEAEs) will be summarized and are defined as those events that 1) occur after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier; 2) any event that is considered study drug-related regardless of the start date of the event; or 3) any event that is presented at baseline but worsens in severity or is subsequently considered drug-related by the investigator.

TEAEs will be summarized by system organ class (SOC) and preferred terms (PT), by NCI CTCAE V4.03 grade, by relationship to study drug, and by action taken. For each TEAE, the percentage of subjects who experience ≥ 1 occurrence of the given event will be summarized. The same summary will be provided for serious TEAEs, and drug-related serious TEAEs, as well as TEAEs leading to treatment discontinuation, death, dose modifications or delays.

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries.

By-subject listings of all AEs (including non-treatment-emergent events), all serious AEs, all deaths that occurred during the study, all TEAEs leading to discontinuation or dose modification of study treatment will be provided. The listings will include: center, subject identifier, treatment group, age, sex, race, adverse event (SOC, PT, and verbatim term) and other information. Additional summaries, listings, subgroup analysis, or subject narratives may be provided, as appropriate.

4.10.2 Adverse Events of Interest

For this study the adverse events of interest are:
4.10.2.1 Elevated Liver Function Tests (LFTs)

- Alanine aminotransferase (ALT) Grade ≥3 (>5.0 x upper limit of normal (ULN))
- Aspartate aminotransferase (AST) Grade ≥3 (>5.0 x ULN)
- Bilirubin Grade ≥3 (>3.0 x ULN)
- Alkaline phosphatase (ALP) Grade ≥ 3 (>5.0 x ULN)
- ALT or AST >3.0 x ULN **WITH** Bilirubin >2.0 x ULN

4.10.2.2 Hepatic Adverse Events

- All hepatic AEs

All hepatic AEs and liver function test (LFT) abnormalities will be reviewed by an Independent Hepatic Expert Committee, at least quarterly, and as needed. Tabulation for AEs of interest will be provided.

Hemorrhagic events, Infection events, and Infusion related reaction events may be included in the scope of the AEs of interest depending on the study safety profile.

4.10.3 Clinical Laboratory Evaluation

In general, laboratory data of hematology and clinical chemistry after the first subsequent anti-cancer therapy, if any, will be excluded in summary due to confounding effect of the therapy.

Summary statistics (N, mean, SD, median, and range) will be calculated for the raw data and for their changes from baseline by scheduled visits, as well as for last value and for the changes from baseline to the last value. Within a cycle, summary statistics of the worst values will be provided. Individual values outside the normal ranges will be identified (by "H" for high and "L" for low) in the data listings displaying the absolute values for each subject.

Displays of over-time summaries will be presented for the following key laboratory parameters: hemoglobin, platelet count, white blood cell count, absolute neutrophil count (ANC), international normalized ratio (INR) (or prothrombin time) and activated partial thromboplastin time (aPTT), sodium, potassium, blood urea nitrogen, creatinine, total bilirubin (with fractionation if abnormal), ALT, AST, ALP, lactate dehydrogenase, and albumin.

Shift tables for each cycle will be produced for selected laboratory parameters, including hemoglobin, platelet count, white blood cell count, ANC, total bilirubin, ALT, AST, and ALP. These tables will summarize by cycle the number of subjects with each baseline CTCAE grade and changes to the maximum CTCAE grade in the cycle. For laboratory parameters without CTCAE grade, shifts from baseline to highest (Low, Normal, High) categories per cycle will be used.

Shift tables from baseline to worst value on treatment (from treatment start to 30 days after last dose or the end of treatment visit date, whichever is later) will also be provided. The worst toxicity grade during the study will be tabulated.

In addition, incidence of persistent (≥ 4 weeks) and severe (grade 3 or higher) cytopenia (thrombocytopenia/neutropenia) and LFT will be evaluated. Time to onset and duration of grade 3 or 4 thrombocytopenia/neutropenia and LFT will be summarized.

4.10.4 Vital Signs, Physical Examination Findings and Other Safety Observations

Over-time summary statistics (n, mean, SD, median and range) of vital signs (temperature, pulse/heart rate, systolic blood pressure and diastolic blood pressure) will be provided for each scheduled visit. A separate summary will be produced for vital signs at baseline, maximum, minimum, change to maximum, change to minimum, last value, and change to last value.

Abnormal baseline physical examination findings will be summarized with the medical history. New or worsened physical examination abnormalities will be analyzed as AEs.

Baseline ECG data will be summarized.

4.10.5 Safety Monitoring: Data Monitoring Committee (DMC) and Independent Hepatic Expert Committee (HEC)

For Part 1 of the study, the DMC performed ad hoc expedited reviews of any ≥Grade 4 hemorrhagic event occurring on the study or any other safety concerns identified by the sponsor.

The first planned DMC safety review meeting for Part 2 of the study will be held after approximately 60 subjects (~30% of the expected enrollment) have been randomized, and subsequent safety review meetings are planned approximately every 6 months thereafter and hold ad hoc meetings if required. The DMC will review unblinded reports for safety as well as efficacy to evaluate risk versus benefit when possible. The summary reports on enrollment, demographic data and baseline characteristics, and conduct of the study will also be reviewed. Separate unblinded biostatistician and programmer team will support the DMC in Part 2.

Data to be reviewed by the DMC periodically are specified in the DMC SAP, which is specifically prepared for DMC reviews.

All hepatic AEs and LFT abnormalities will be reviewed by an Independent Hepatic Expert Committee (HEC), at least quarterly, or as needed. Full details of the DMC and HEC procedures and processes can be found in the DMC Charter and HEC Charter.

4.11 Other Analyses

4.11.1 Study impacts due to COVID-19 pandemic

Protocol Amendment 4 is issued in consideration of the COVID-19 pandemic. The following data will be summarized as appropriate for all subjects and by treatment group to evaluate the impacts on study due to the COVID-19 pandemic. By-subject listings will be provided as well.

4.11.1.1 Evaluation of the COVID-19 impacts on efficacy endpoints

- Impacts of delayed or reduced transfusions on 8-week, 24-week TI, time to and duration of TI, HI-E (transfusion reduction):
    - Intended transfusion types, intended transfusion units if reduced, the indications of transfusion, and reasons of delay along will be summarized and listed.
    - Number and percentage of subjects with delayed or reduced transfusions.
- Impacts of delayed/missed visit and assessment on other key secondary endpoints, e.g. HI-E (Hb), disease response, PFS, and time to AML
    - incidence will be summarized by parameter and listed.

4.11.1.2 Evaluation of the COVID-19 impacts on safety endpoints

- Death and treatment discontinuation will be summarized and listed.
- TEAEs related to COVID-19 will be summarized and listed similarly as other TEAEs.
- Delayed/missed lab will be summarized by lab parameter and listed.
- Delayed cycle/dose will be summarized and listed.

4.11.2 Pharmacokinetics/Pharmacodynamics (PK/PD)

Included in the secondary objectives of this study is to characterize PK of imetelstat in study subjects. Specifically, individual-specific PK parameters will be estimated based on observed imetelstat concentrations and a previously established population PK model. Included in the exploratory objectives of this study is to evaluate potential relationship between imetelstat exposure (e.g., C_{max} and AUC) and clinical efficacy, safety/hematology, and biomarker endpoints.

Separate analysis plan document will be provided by the PK/PD analysis group and details will be provided in a separate report with analysis results.

4.11.3 Ventricular Repolarization substudy (Part 2)

Additional ECG analysis and exposure-response analysis for the Ventricular Repolarization substudy in Part 2 will be provided in the Ventricular Repolarization Substudy Cardiac SAP and will be performed separately from the primary analysis of 170 subjects in the main study of Part 2. Safety data and available data from efficacy will be summarized based on the main study SAP.

4.11.4 Medical Resource Utilization (Part 2)

The effect of treatment on medical resource utilization is listed as the secondary objective. Medical resource utilization data, associated with medical encounters, will be collected in the eCRF in Part 2 by the investigator and study-site personnel for all subjects throughout the study including the long-term follow up after termination of treatment. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will be used to conduct the health economic analyses and will include:

- Frequency and duration of hospitalization (total days length of stay, including duration by wards; e.g. intensive care unit)
- Outpatient medical encounters and treatments (including physician or emergency room visits, selected tests and procedures, and medications)

Frequency and duration of hospitalization, frequency of emergency room visit and specialty physician visit will be listed and summarized where appropriate. Results may be grouped by treatment, subgroups, or clinical response.

Medical resource utilization data collection is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

4.11.5 Biomarkers

Biomarker related study objectives are:

- To evaluate pharmacodynamic biomarkers such as TA, TL and hTERT and to explore the association between baseline results and clinical response
- To evaluate change of cytogenetic abnormalities and explore the association between baseline cytogenetic status and clinical response
- To evaluate baseline mutational status and mutation changes during treatment for exploring the association with clinical response
- To explore the effects of imetelstat on immune profiles through immunophenotyping (Part 1 only)
- To evaluate the exposure-response relationship between pharmacokinetics and pharmacodynamic biomarkers, efficacy and safety

Biomarker measures and the change from baseline will be listed, tabulated, and plotted where appropriate. Subjects may be grouped by treatment (Part 2), biomarker subgroups, or clinical response. Correlation of baseline or changes of biomarkers with clinical parameters will be analyzed by appropriate statistical methods (e.g., parametric or non-parametric, univariate or multivariate). A separate biomarker SAP may be prepared, and results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

Biomarker assessments are not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

4.11.6 Patient Reported Outcome (PRO) Measures (Part 2 only)

In main study of Part 2 of the study, PROs will be assessed at the visits according to Time and Events Schedule in the protocol using 4 measures: the QUALMS, the FACT-An, the EQ-5D-5L, and the PGIC. Specifically, the PROs will be collected at baseline, at each visit during treatment, at the end of treatment (EOT) visit and at each visit during posttreatment phase. The protocol assessment questionnaires need to be done in the same order at each visit and for each subject to ensure that the subject is answering these as consistently as possible.

Interim blinded data will be used to establish psychometric properties, such as construct validity, and responsiveness and reliability, for selected scales, e.g. QUAMLS and FACT-An. Minimal important difference (MID) will be estimated using both anchor-based (e.g., PGIC or clinical anchor) and distribution-based methods. Preliminary pooled cumulative distribution curve will be plotted. A separate PRO validation analysis plan will be prepared, and results of validation analyses will be presented in a separate report.

Geron considered that the benefit of imetelstat in terms of transfusion burden reduction and independence would not be at the cost of less controlled core symptoms of LR MDS. Based on the findings of the PRO measurement strategy in the psychometric analyses on the interim blinded data, the assessment of fatigue using the FACIT-Fatigue score would be the concepts of interest (COI) measured for symptom control, however, the sample size of the study does not provide sufficient power to demonstrate the absence of deterioration of fatigue in imetelstat versus placebo treated patients in the specific context of use of the MDS3001 study.

For these reasons, Geron does not plan to use the MDS3001 study to formally demonstrate the benefit of imetelstat compared with placebo in terms of PRO endpoint and the PRO data will not be used for the specification of secondary endpoints of the study. Instead, the PRO data will be included as exploratory endpoints, with descriptive analyses to document the change in PRO scores targeting the COIs over the course of the study.

PRO evaluation is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

4.11.6.1 EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [7, 8]. The scores for the 5 separate questions are categorical and cannot be analyzed as ordinal numbers. However, the scores for the 5 categorical dimensions will be used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D in this study. Other country specific weights may be used when needed.

4.11.6.2 FACT-An (version 4)

The FACT-An (version 4) [9] is one of the scales from the Functional Assessment of Chronic Illness Therapy Measurement System. It consists of the FACT-G (General version) and 20 questions labeled “Additional concerns” which measure anemia/fatigue.

The FACT-G (version 4) [10] is a 27-item compilation of general questions divided into 4 primary quality of life domains:

- Physical well-being (PWB)
- Social/family well-being (SWB)
- Emotional well-being (EWB)
- Functional well-being (FWB)

The FACT-G (version 4) is considered appropriate for use with subjects with any form of cancer and has also been used and validated in other chronic illness conditions. The additional items of the FACT-An, Anemia Subscale (AnS), allow for constructing a Fatigue subscale. The subject is asked to rate the scale items as it applies to the past 7 days, on a 5-point scale (0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = Very much). Negatively stated items will be reversed by subtracting the response from 4. After reversing the proper items, items are summed to a total to generate a score on a (sub) scale [9, 10].

- FACT-An Trial Outcome Index (TOI) = PWB + FWB + AnS
- FACT-G total score = PWB + SWB + EWB + FWB
- FACT-An total score = PWB + SWB + EWB + FWB + AnS

4.11.6.3 QUALMS Questionnaire

The QUALMS [6] is a 38-item measure that assesses health-related quality-of-life for subjects with MDS. The 33-item total score, as well as the 14-item physical burden (QUALMS-P), 3-item benefit-finding (QUALMS-BF), and 11-item emotional burden (QUALMS-E) subscales will be analyzed. There are also 5 single-item questions presented at the end of the measure that do not form part of the overall scale, as they are not applicable to all subjects with MDS. In addition, the data of another MDS subjects interview project indicated several common symptoms can be measured in six items of QUALMS. These 6 items will form the symptom score of QUALMS.

Higher QUALMS scores represent better MDS-related quality of life. Question responses are assigned numerical values of 0, 25, 50, 75 or 100, suitable for a 5-point scale. For 29 items, 0 = Always while 100 = Never. The remaining 4 items are reverse-scored with 100 = Always and 0 = Never.

The possible range of scores for both the overall scale and the 4 subscales is 0 – 100. After scoring all items:

- Total QUALMS score: mean of all primary questions 1–33
- QUALMS-P: mean of questions 6, 7, 8, 9, 10, 11, 13(R), 18, 20, 23, 24, 25, 26, 33
- QUALMS-BF: mean of questions 17, 29 & 30 (all reverse-scored)
- QUALMS-E: mean of questions 1, 2, 3, 4, 5, 12, 14, 15, 19, 27, 32
- Symptom score of QUALMS: mean of questions 6, 8, 13, 18, 23, 33

4.11.6.4 PGIC Questionnaire

The PGIC is used to capture the patient's perspective of improvement or decline in MDS over time. The PGIC has a 7–point response scale ranging from 1 (very much improved) to 7 (very much worse), with 4 representing no change.

4.11.6.5 Analysis Methods

Descriptive Analysis

Descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum) at baseline, each post-baseline time point and change from baseline will be reported by treatment group for each of four PRO measures, including QUALMS total scores, subscale scores (QUALMS-BF, QUALMS-E, and QUALMS-P), symptom score of QUALMS, FACT-An subscale scores (PWB, SWB, EWB, FWB, and AnS), FACT-An summary scores (FACT-An TOI, FACT-G total score, and FACT-An total score), PGIC, EQ-5D visual analogue scale and weighted utility score.
More detailed PRO analysis plan will be presented in a separate PRO SAP, and results may be presented a separate report.

4.12 Determination of Sample Size

Approximately 270 subjects (57 subjects already enrolled in Part 1, approximately 170 subjects in the main study of Part 2, and approximately 45 subjects in Ventricular Repolarization substudy of Part 2) will be enrolled in the study.

On the basis of historical data, RBC TI rate is expected to be approximately 7.5% [15, 16] in subjects with low or intermediate-1 risk MDS without any active treatment. The RBC TI rate with imetelstat treatment is expected to be approximately 30% based on preliminary data from [17]. The futility criteria before Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (eg, transfusion reduction, erythroid improvement). The initial cohort of 32 subjects enrolled into Part 1 was expanded with Amendment 2 to include an additional 25 subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide who meet the revised entrance criteria, for a total of 57 subjects in Part 1.

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat, Part 2 of the study will be initiated. If the RBC TI rate of 30% with imetelstat treatment is true, the probability of passing the futility criterion is 97%. All available data will be used to support the decision.

In the main study of Part 2, approximately 170 subjects will be randomized in a 2:1 ratio to receive either imetelstat or placebo the main study of Part 2. Using a 2:1 ratio randomization and a 2-group continuity corrected Chi square test with 0.05 (2-sided) significance level, 150 subjects are needed to achieve a power of approximately 88% to detect the difference between an RBC TI rate of 30% in the imetelstat group and an RBC TI rate of 7.5% in the placebo group. After correction for a 10% drop-out rate, a total of approximately 170 subjects (115 in imetelstat group and 55 in placebo group) will be needed. The overall study power from Part 1 and the main study of Part 2 is approximately 85%.

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